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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : HOWSON, William [GB/GB]; Parke-Davis Research Unit, Addenbrookes Hospital, Cambridge CB2 2QB (GB).

(74) Agent: SMITHKLINE BEECHAM; Corporate Patents, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

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(54) Title: S-(3-(4(5))-IMIDAZOLYL)PROPYL)ISOTHIOUREA AS SELECTIVE TRHISTOMINE H3 RECEPTOR ANTAGONIST

(57) Abstract

Use of an isothiourea derivative as a histamine H_3-antagonist.

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S-(3-(4(5))-IMIDAZOLYL)PROPYL)ISOTHIOUREA AS SELECTIVE TRHISTOMINE H3 RECEPTOR ANTAGONIST

The present invention relates to pharmaceutical compositions comprising an imidazole derivative, their use in the manufacture of medicaments having histamine H_3-antagonist activity and a method of blocking histamine H_3-receptors by administering them.

Histamine, a physiologically active compound endogenous in mammals, exerts its action by interacting with certain sites called receptors. One type of receptor is known as a histamine H_1-receptor (Ash and Schild, Brit. J. Pharmac. Chemother. 27 427 (1966)) and the actions of histamine mediated through these receptors are blocked by H_1-antagonists such as mepyramine. A second type of receptor is known as the histamine H_2-receptor (Black et al., Nature 1972, 236, 385) which is not blocked by mepyramine but by H_2-antagonists such as burimamide or cimetidine. A third type of receptor known as the histamine H_3-receptor has more recently been identified (e.g. Arrang et al., Nature 1987, 327 , 117 and Van der Werf et al., (1989) Trends Pharmacol. Sci. 10, 159) which is stimulated by H_3-agonists such as (R)-α-methylhistamine and blocked by H_3-antagonists such as thioperamide.

US-A-3759944 discloses isothiourea derivatives which are described as acting at histamine receptors other than the H_1-receptor and are of utility in inhibiting certain actions of histamine which are not inhibited by H_1-antagonists such as the inhibition of histamine-stimulated secretion of gastric acid. A particular isothiourea described is S-[3-(4(5)-imidazolyl)propyl]isothiourea dihydrobromide. This compound is also disclosed in Eur. J. Med. Chem.-Chim. Ther., 21(4), 305-9 (1986) wherein it is described as being a weak partial H_1-agonist and a weak H_2-agonist.

It has now been discovered that the above named imidazole compound is a highly potent selective histamine H_3-antagonist.

Accordingly the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and S-[3-(4(5)-imidazolyl)propyl]-isothiourea or a pharmaceutically acceptable salt thereof in an amount sufficient to block selectively histamine H_3-receptors.

In another aspect the present invention provides the use of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof in the manufacture of a medicament having histamine H_3-antagonist activity.

In a further aspect this invention provides a method of blocking histamine H_3-receptors in a host in need thereof which comprises administering an effective amount to block said receptors of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable salts include those formed with hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, citric, maleic, lactic, ascorbic, fumaric, oxalic, methanesulphonic and ethanesulphonic acids.

In order to use S-[3-(4(5)-imidazolyl)propyl]-isothiourea or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

S-[3-(4(5)-imidazolyl)propyl]isothiourea and its pharmaceutically acceptable salts can be administered in standard manner for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

S-[3-(4(5)-imidazolyl)propyl]isothiourea and its pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations can be used. Examples of such carriers include magnesium stearate, starch, celluloses, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions can be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinyl-pyrrolidone, 2-pyrrolidone, cyclodextrin, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example

a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 50 mg, and preferably from 1 mg to 25 mg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 25 mg, of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for oral administration is suitably about 0.1 mg to 200 mg, preferably 1 mg to 100 mg, of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.1 mg to 100 mg, for example about 1 mg to 40 mg, of S-[3-(4(5)-imidazolyl)-propyl]isothiourea or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required for example from 1 to 4 times a day or by infusion. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the

compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. For example diazepam may be included in pharmaceutical compositions comprising S-[3-(4(5)-imidazolyl)propyl]-isothiourea.

The histamine H_3-antagonist activity of S-[3-(4(5)-imidazolyl)propyl]isothiourea was assessed by a method similar to that described by Trzeciakowski (1987), J. Pharmacol. Exp. Ther., 243, 874-880. Inhibition of the electrically evoked twitch responses of the guinea-pig ileum by histamine H_3-receptor agonists was studied by addition of graded concentrations of (R)-α methyl-histamine (in volumes of 25 µl or 79 µl) to the organ bath in a sequential manner. Each concentration of agonist was washed out of the bath when the response had reached equilibrium. A four minute period was allowed between each addition of the compound. In the antagonist studies a ten minute period was used for the antagonist equilibration time. Antagonist activity was quantified by the ability of the compound to block the inhibitory effect of (R)-α-methylhistamine on the twitch response.

The concentration of compound which caused 50% antagonism of the inhibitory effect of (R)-α-methylhistamine on the twitch response is given as the IC_{50} (nM). The following results were obtained:

Compound of formula (1)	IC_{50} (nM)
S-[3-(4(5)-imidazolyl)-propyl]isothiourea	7
Thioperamide	6.4

The activity of S-[3-(4(5)-imidazolyl)propyl]-isothiourea at the histamine H_1- or H_2-receptor was assessed substantially as described by Parsons et al., Agents and Actions, 1976, 7(1), 31. Concentrations up to 10^{-5} M had no agonist or antagonist activity at histamine H_1- and H_2-receptors.

The above results indicate that S-[3-(4(5)-imidazolyl)-propyl]isothiourea is a highly potent selective histamine H_3-antagonist, being about 1000 times more potent at the histamine H_3-receptor than at either the histamine H_1- or H_2-receptor.

Antagonists of the histamine H_3-receptor are believed to stimulate the synthesis and release of neurotransmitters such as histamine and are therefore likely to increase neurotransmitter release in the digestive tract and in the nervous, cardiovascular and immune systems. They are likely to have a psychotropic action and have utility in cognitive disorders including the treatment of Alzheimer's disease and age-associated memory impairment.

The following example serves to illustrate a pharmaceutical composition of this invention.

Example 1

A pharmaceutical composition for oral administration is prepared containing:

		% by weight
A	S-[3-(4(5)-imidazolyl)propyl]isothiourea	55
	Dibasic calcium phosphate dihydrate	20
	Approved colouring agent	0.5
	Polyvinylpyrrolidone	4.0
		% by weight
B	Microcrystalline Cellulose	
	Maize Starch	8.0
	Sodium glycollate	4.0
	Magnesium Stearate	0.5

by mixing together the ingredients A (substituting lactose or microcrystalline cellose for dibasic calcium phosphate dihydrate if desired), adding a concentrated solution of polyvinylpyrrolidone and granulating, drying and screening the dried granules; adding the ingredients B to the dried granules and compressing the mixture into tablets containing 10 mg, 25 mg or 50 mg of the free base.

Claims

1. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof in an amount sufficient to block selectively histamine H_3-receptors.

2. A pharmaceutical composition according to claim 1 adapted for oral administration wherein each dosage unit comprises from 0.1 mg to 50 mg of S-[3-(4(5)-imidazolyl)-propyl]isothiourea.

3. A pharmaceutical composition according to claim 1 adapted for parenteral administration wherein each dosage unit comprises from 0.1 mg to 25 mg of S-[3-(4(5)-imidazolyl)propyl]isothiourea.

4. The use of S-[3-(4(5)-imidazolyl)propyl]-isothiourea or a pharmaceutically acceptable salt thereof in the manufacture of a medicament having histamine H_3-antagonist activity.

5. A method of blocking histamine H_3-receptors in a host in need thereof which comprises administering an effective amount to block said receptors of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01299

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/415

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	US,A,3759944 (J.W. BLACK et al.) 18 September 1973, see whole document (cited in the application)	1-3
A		4,5

A	Agents and Actions, vol. 18, nos. 1/2, 1986, Birkhäuser Verlag, (Basel, DE), G.J. STERK et al.: "The influence of guanidino and isothiourea groups in histaminergic compounds on H2-activity", pages 137-140, see whole document, especially page 138, last paragraph	1-5

A	EP,A,0197840 (INSERM) 15 Oktober 1986, see whole document	1-5
	--- -/-	

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24-09-1992	20. 10. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

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III. D CUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °.	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0420396 (SMITH KLINE & FRENCH LAB. LTD) 3 April 1991, see whole document	1-5

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201299 SA 62460

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 14/10/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3759944	18-09-73	US-A- 3818097	18-06-74
EP-A- 0197840	15-10-86	FR-A- 2579596	03-10-86
		JP-A- 61267574	27-11-86
		US-A- 4707487	17-11-87
EP-A- 0420396	03-04-91	JP-A- 3058924	14-03-91
		US-A- 5047418	10-09-91